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ORIGINAL INVESTIGATION

The PDE5 inhibitor vardenafil does not affect auditory sensory gating in rats and humans

O. A. H. Reneerkens · A. Sambeth · M. A. Van Duinen · A. Blokland · H. W. M. Steinbusch · J. Prickaerts

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Abstract
Rationale Sensory gating is an adaptive mechanism of the brain to prevent overstimulation. Patients suffering from clinical disorders such as Alzheimer's disease or schizophrenia exhibit a deficit in gating, which indicates not only an impairment in basic information processing that might contribute to the cognitive problems seen in these patients. Phosphodiesterase type 5 inhibitors (PDE5-Is) have been shown to improve cognition in rodents in various behavioural tasks and might consequently be an interesting target for cognition enhancement. However, the effects of PDE5-Is on sensory gating are not known yet.
Objectives This work aims to study the effects of PDE5 inhibition on auditory sensory gating in rats and humans.
Methods In the rat study, vehicle or 0.3–3 mg/kg of the PDE5-I vardenafil was given orally 30 min before testing and electrode locations were the vertex, hippocampus and the striatum. The human subjects received placebo, 10–20 mg vardenafil 85 min before testing and sensory gating was measured at the cortex (Fz, Fcz and Cz) electrodes.
Results Significant gating was only found for the N1 component in rats while all three peaks P1, N1 and P2 showed gating in humans, i.e. the response to the second sound click was decreased as compared with the first for these deflections. Administration of vardenafil did neither have an effect on sensory gating in rats nor in humans.
Conclusions These findings imply that positive effects of PDE5 inhibition on cognition are not mediated by more early phases of information processing.

Keywords Sensory gating · Translational · PDE5 · Vardenafil · Basic auditory information processing · EEG

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Introduction

Sensory gating is an automatic process involved in information processing. More specifically, it is an adaptive mechanism of the central nervous system that prevents overstimulation of higher cortical areas and helps filtering sensory information (e.g. Cromwell et al. 2008). The standard paradigm assessing this mechanism consists of two identical auditory stimuli that are presented with an interstimulus interval (ISI) between 0.5 and 2 s and an intertrial interval (ITI) of at least 8 s (Cromwell et al. 2008; Hajos 2006). In healthy individuals—humans as well as animals—the response to the second stimulus (S2) will be smaller than the response to the first stimulus (S1). Of note, the duration of the ISI is crucial; if it is shorter than 0.5 s or longer than 2 s, sensory gating will not be elicited. Extensive research has shown that the process of sensory gating is disrupted in patients suffering from clinical disorders including schizophrenia and Alzheimer's disease (e.g. Adler et al. 1982; Ally et al. 2006; Javitt 2009; Jessen et al. 2001).

The responses evoked by this auditory sensory gating paradigm can be assessed using electroencephalographic (EEG) and event-related potential (ERP) measurements. In humans, the P50, also known as P1, is considered to be the main ERP component related to sensory gating (e.g. Chang

et al. 2011; Dalecki et al. 2011). In addition, the N100 (N1) and P200 (P2) might also be affected (e.g. Boutros et al. 2009; Lijffijt et al. 2009). There is still a debate about which ERP component in rats is possibly the functional equivalent of the P50 in humans. Some researchers suggest that the P13 (P1) (e.g. Miyazato et al. 1999) is the most suitable candidate, whereas others assume it is the N40 (N1) or P60 (P2) (e.g. Mears et al. 2006; Zhou et al. 2008). It has also been suggested that the entire P1-N1-P2 complex is involved in the auditory sensory gating paradigm in rats just as in humans (e.g. Broberg et al. 2010; Mears et al. 2009).

Recently, phosphodiesterases (PDEs) gained increased attention as a promising target for cognition enhancement. Depending on the enzyme subclass, they selectively hydrolyze the second messengers cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) (Bender and Beavo 2006). It has been shown that drugs that prevent the breakdown of these PDEs, the so-called PDE inhibitors (PDE-Is), improve cognition in animals in a wide range of behavioural tasks (for review, see Reneerkens et al. 2009). Since the cGMP-specific phosphodiesterase type 5 inhibitors (PDE5-Is) are clinically approved for treatment of erectile dysfunction, they can be tested in animals as well as humans, which makes them particularly interesting from a translational perspective. It has already been shown that PDE5 inhibition has a positive effect on a variety of cognitive processes in animals, including learning (e.g. Devan et al. 2006, 2007), memory (e.g. Prickaerts et al. 2002b; Reneerkens et al. 2012; Rutten et al. 2007; van Donkelaar et al. 2008), executive functioning and response inhibition (Rutten et al. 2008). In contrast, only a limited number of studies investigated the effects of PDE5-Is on cognition in humans. Three of those studies did not show any effects of PDE5 inhibition on cognitive performance in healthy adults (Grass et al. 2001; Schultheiss et al. 2001) and patients with schizophrenia (Goff et al. 2009) respectively. Yet, EEG measurements in healthy adults indicated that there might be an effect of treatment with the PDE5-I sildenafil on attention (Schultheiss et al. 2001). Interestingly, it has recently been demonstrated that repeated dosing of the PDE5-I Udenafil improves the cognitive performance of patients suffering from a erectile dysfunction on a modified version of the mini-mental state examination and an assessment battery addressing frontal executive functioning (Shim et al. 2011).

In our present study, we investigated the effects of PDE5 inhibition on sensory gating in rats and humans. Rats were included because of the extensive learning- and memory-enhancing effects that have already been reported in rodents while to our knowledge basic auditory information processing has not been studied yet after PDE5 inhibition. Likewise, the effects on sensory gating in humans were studied to gain further insight into the effects of PDE5 inhibition on information processing in humans, but also to see whether the drug effects found in rodents can be translated to the human situation and vice versa. It has indeed been shown that the ERPs of humans and rats show a substantial amount of similarities (e.g. Sambeth et al. 2003). Based on these findings, we expect that the effects of drugs on these ERPs are comparable between humans and animals (Maxwell et al. 2004). First, we tested whether our paradigm elicited sensory gating. Next, the effects of the PDE5-I vardenafil on sensory gating were investigated. It was chosen to test 0.3–3 mg/kg vardenafil in rats since this dose range is mostly used in a wide array of behavioural tasks (e.g. Prickaerts et al. 2004, 2002b; Reneerkens et al. 2012; Rutten et al. 2007, 2009). We included the vertex, hippocampus and striatum as electrode locations because of their involvement in sensory gating. The vertex was chosen to represent the cortex since the EEG signal at this location is relatively comparable to that at a similar location in humans. We recorded EEG from the Fz, Fcz and Cz (vertex) locations in humans (see Jasper 1958) and used 10 and 20 mg because these are the dosages commonly used in humans.

Materials and methods

Animal study

Animals

All experimental procedures were approved by the local ethical committee for animal experiments of Maastricht University and met governmental guidelines. Thirteen 3-month-old male Wistar rats (Harlan, The Netherlands) were used with average body weights of 385 g (±12.50). The animals were housed individually in standard Makrolon cages on sawdust bedding in an air-conditioned room (about 20 °C). They were kept on a 12/12-h reversed light/dark cycle (lights on from 1900 to 0700 hours) and had free access to food and water. The rats were housed in the same room as where they were tested. All testing was done between 0900 and 1800 hours in a shielded Skinner box.

Surgery and EEG recordings

The animals received 0.1 ml/kg Temgesic (Schering-Plough B.V., Utrecht, The Netherlands) subcutaneously 30 min before surgery as analgesia. Forene isoflurane (Abbott B.V., Hoofddorp, The Netherlands) was used as a general inhalation anaesthetic. After the animal was placed into the stereotactic apparatus and an incision was made to expose the skull, lidocaine was applied as additional local anaesthesia. Next, bregma was identified and the electrodes were placed in the striatum (AP, 0.48; ML, −3.0; and DV, −5.0), dorsal

hippocampus (AP, −2.8; ML, −1.8; and DV, −2.6) and vertex (AP, −3.5; ML, −1.0; and DV, −1.0) (Paxinos and Watson 1998). The reference and ground electrodes were both placed in the cerebellum. The electrodes and the connector were fixed to the skull by using three screws and Paladur denture acrylic (Heraeus Kulzer, Hanau, Germany). The animals were given at least 2 weeks to recover from the surgery.

In the first week after recovery, the animals were handled daily and adapted to the procedure, i.e. they were connected to the EEG set-up and allowed to explore the Skinner box in which the recording would take place. In addition, the rats were adapted to per os (p.o.) administration procedures by saline injections (2 ml/kg). Next, the control condition was tested, i.e. animals were treated with placebo; this was tested twice and averaged for the statistical analysis. Subsequently three doses of the PDE5-I vardenafil were randomly tested (0.3, 1 and 3 mg/kg, p.o.). The sensory gating paradigm consisted of 70 pairs of auditory stimuli which were presented with stimulus duration of 10 ms, ISI of 500 ms and ITI of 6–10 s. The EEG signal was sampled at 1,000 Hz, filtered between 1 and 133.5 Hz and stored on a personal computer. The stimuli were 2,500 Hz clicks with a sound intensity of 80 dB. Since the animals were tested in a sound-attenuated room with a maximal background noise level of 20 dB, the level of our stimulus salience was approximately 60 dB. After the study was finished, the animals were killed by decapitation and the brains were taken out. The brains were stored in 4 % formaldehyde at 4–6 °C until electrode localisation took place.

Treatment

Vardenafil was first dissolved in 1.5 ml ethanol with 2 % Tween 80. After extraction of ethanol via vaporisation under N2 gas, the compounds were dissolved in 0.5 % methylcellulose. The compound was tested at a dose of 0.3–3 mg/kg and administered by oral gavage (2 ml/kg) 30 min before testing. Vardenafil was kindly donated by BAYER (Wuppertal, Germany). The experimenter was blind to the compound and doses tested. All animals were treated with each condition once, except for the control condition (placebo), which was tested twice as part of the training.

Electrode localisation

In order to verify the localisation of the striatal and hippocampal electrode, coronal slices (50 μm) were made with a vibratome and put on glass slides. Next, a haematoxylin and eosin staining was applied and the slices were inspected under a microscope. If the localisation of the hippocampal or striatal electrode could not be verified and/or the raw data did not show the typical delta and theta waves in the hippocampal EEG, the animal was excluded for that part of the analyses (number of animals mentioned in the 'Results'). Since the vertex electrode measures the EEG signal at the cortical surface, there was no need for localisation.

Statistical analysis

Segments between 100 ms before until 500 ms after stimulus onset were made for each stimulus type (S1 and S2) separately, using the last 100 ms before onset as baseline. High- (1 Hz) and low-pass (30 Hz) filters were applied. The segments were visually checked and removed from the dataset if a movement artefact occurred within 500 ms after stimulus presentation. Both the grand average (all animals) and the individual data (single animal) were used to determine the auditory evoked potential (AEP) components. In general, P1 was defined as most positive value between 20 and 50 ms after stimulus onset. N1 was the most negative value between 50 and 80 ms for the vertex and between 40 and 70 ms for the striatum and hippocampus. Finally, P2 was defined as most positive value between 65 and 105 ms for the vertex and between 55 and 90 ms for the striatum and hippocampus.

General linear models (GLM) repeated measures were used to analyse the amplitudes of the components. First, the responses to the S1 and S2 were compared for the vehicle condition to see whether sensory gating occurred. Next, the responses to the PDE-Is conditions were compared with placebo condition for each stimulus (treatment) separately as well as for both stimuli together (treatment × stimulus). In case of a statistically reliable effect, comparisons between means of the conditions were analysed in more detail using post hoc Bonferroni t tests ($P<0.05$). Two animals were excluded from the analysis of the vertex and the striatum electrodes because of no reliable EEG signal.

Human study

Subjects

All experimental procedures were approved by the independent Ethics Committee of Maastricht University and the Academic Hospital Maastricht (The Netherlands). Eighteen participants (21±0.7 years old; five males) were recruited through advertisements at Maastricht University. They had to be willing to sign an informed consent and were paid for their participation.

The subjects' physical and mental health was checked by a physician by means of a standard medical questionnaire and a medical examination. Subjects were

excluded if they suffered from or had a history of cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, haematological or psychiatric illness. Other exclusion criteria were excessive drinking (>20 glasses of alcohol containing beverages a week), pregnancy or lactation, use of medication other than oral contraceptives, use of recreational drugs from 2 weeks before until the end of the experiment and any sensory or motor deficit which could reasonably be expected to affect test performance. In addition, subjects who had a first-degree relative with (history of) a psychiatric disorder, were excluded as well. The participants could leave the study at any given time without any consequence.

EEG recordings

An EEG cap was used to place a set of 32 EEG electrodes according to the international 10–20 system (Jasper 1958). Only the Fz, Fcz and Cz locations were used in the current study since it has been demonstrated previously that midline electrodes show better P50 sensory gating than left/right hemispheric sites, especially the Cz (vertex) and Fcz electrodes (Wan et al. 2006). In addition, the Fz electrode has been demonstrated to show a similar amount of P200 gating and was therefore included as well (Wan et al. 2007). A reference and a ground were placed at the linked mastoids and at the forehead, respectively. Eye movements were detected by horizontal and vertical electro-oculogram (EOG) recordings. Before electrode attachment, the positions were cleaned with alcohol and slightly scrubbed with a gel in order to provide a good measurement. Both EEG and EOG were filtered between 0.01 and 100 Hz and sampled at 1,000 Hz.

The sensory gating paradigm consisted of 60 pairs of identical auditory stimuli with a duration of 3 ms and intensity of 80 dB. Since testing took place in a sound-attenuated room with a maximal background noise level of 20 dB, the stimulus salience was approximately 60 dB. The interval between the first (S1) and the second (S2) stimulus was 500 ms; the interval between pairs was randomised between 6 and 10 s. The subjects were familiarised with this test during a training session.

Design and treatment

The study was conducted according to a double-blind, placebo-controlled, three-way cross-over design. Order of treatments was balanced over three test days and separated by a washout period of at least 7 days. The balancing of the treatment order was accomplished by counterbalancing.

Treatment consisted of a placebo, 10 or 20 mg vardenafil HCl (Levitra) and was within the range of dosages (5–20 mg) approved for human use (EMEA 2008). Previous studies have shown that peak plasma levels of vardenafil were reached 30–120 min (median, 60 min) after a single dose of 20 mg vardenafil; the terminal half-life was around 4–5 h (EMEA 2008). Since this study was part of a larger experiment consisting of multiple tasks, our sensory gating paradigm was tested 85 min after drug treatment. The drugs were ingested orally and combined with a low-fat breakfast, because fatty food might affect the absorption of vardenafil. The experimenter and subjects were blind to the compound and doses tested.

Medical questionnaire

A medical questionnaire was presented to the subjects twice each testing day: directly before ingesting the compound/placebo (baseline) and approximately 100 min later (during a short break) (treatment). This questionnaire addressed 31 physical complaints, including headache, nausea, dry mouth, blurred vision and dizziness. Participants could indicate on a 4-point scale to what extent these items applied to their physical well-being (0=not present; 3=extremely present). The difference between the baseline and treatment scores were analysed by using GLM repeated measures.

Statistical analysis

Segments between 100 ms before until 500 ms after stimulus onset were made for each stimulus type (S1 and S2) separately, using the last 100 ms before onset as baseline. High-pass (1 Hz) and low-pass (30 Hz) filters were applied. The segments were visually checked for EOG activity and other artefacts and removed from the dataset if an artefact occurred during the first 500 ms after stimulus presentation. The grand average was used to determine the AEP components. P1 was defined as most positive value between 60 and 90 ms after stimulus onset, N1 as most negative value between 85 and 150 ms and P2 as most positive value between 140 and 250 ms.

GLM repeated measures were used to analyse the amplitudes of the AEP components at the Fz, Fcz and Cz locations (channel). First, the responses to the S1 and S2 were compared for the placebo condition to see whether sensory gating occurred. Next, the responses to the vardenafil conditions were compared with the placebo condition for each stimulus separately (treatment × channel) as well as for both stimuli (treatment × stimulus × channel). In case of a statistically reliable effect,

comparisons between means of the conditions were analysed in more detail using post hoc Bonferroni *t* tests ($P<0.05$). One subject was excluded from the analyses because of an incomplete dataset.

Results

Animal study

Effects of placebo on sensory gating in rats

The effects of placebo treatment on sensory gating are depicted in Fig. 1. GLM repeated measures showed that the N1 peak is less negative in response to S2 than S1 at the vertex ($F_{1,\ 10}=11.39$; $P<0.01$). In the hippocampus, the N1 peak was also less negative after the presentation of S2 than S1 ($F_{1,\ 12}=6.20$; $P<0.05$).

Effects of PDE5 inhibition on information processing in rats

No effects of vardenafil treatment (0.3–3 mg/kg (p.o.) 30 min before testing) on the P1, N1 and P2 were found in the *hippocampus* and *striatum* as well as for the P1 and P2 in the *vertex*. Vardenafil seemed to affect the N1 in the vertex ($F_{2.36,\ 23.62}=3.31$; $P<0.05$), but further post hoc analysis revealed no difference between treatment conditions. This is illustrated in Fig. 2 showing the results of vardenafil treatment on the peaks and locations that showed sensory gating in the placebo condition (see Fig. 1) (N1 vertex—condition*stimulus ($F_{1.40,\ 13.99}=0.33$, n.s.); *hippocampus*—condition*stimulus ($F_{1.90,\ 22.81}=0.39$, n.s.), condition ($F_{1.97,\ 23.69}=1.87$, n.s.)).

Human study

Effects of placebo on sensory gating in humans

The effects of placebo treatment on sensory gating are depicted in Fig. 3. GLM repeated measures showed that there is an interaction between stimulus and channel for the P1 ($F_{1.08,\ 17.22}=4.60$; $P<0.05$), N1 ($F_{1.21,\ 19.36}=15.25$; $P<0.001$) and P2 ($F_{1.21,\ 19.39}=24.61$; $P<0.001$) peaks. Further analyses for the three channels separately showed that the P1 was less positive after S2 than S1 at the Fcz ($F_{1,\ 16}=5.69$; $P<0.05$) and Cz ($F_{1,\ 16}=7.13$; $P<0.05$). In addition, the N1 was less negative and the P2 less positive after the S2 than S1 at the Fz (N1—$F_{1,\ 16}=59.55$; $P<0.001$; P2—$F_{1,\ 16}=34.94$; $P<0.001$), Fcz (N1—$F_{1,\ 16}=56.32$; $P<0.001$; P2—$F_{1,\ 16}=50.08$; $P<0.001$) and Cz (N1—$F_{1,\ 16}=49.48$; $P<0.001$; P2—$F_{1,\ 16}=52.73$; $P<0.001$).

Effects of PDE5 inhibition on information processing in humans

The effect of vardenafil (10–20 mg (p.o.) 85 min before testing) administration on the ERP components in the placebo condition (see Fig. 3) are shown in Fig. 4.

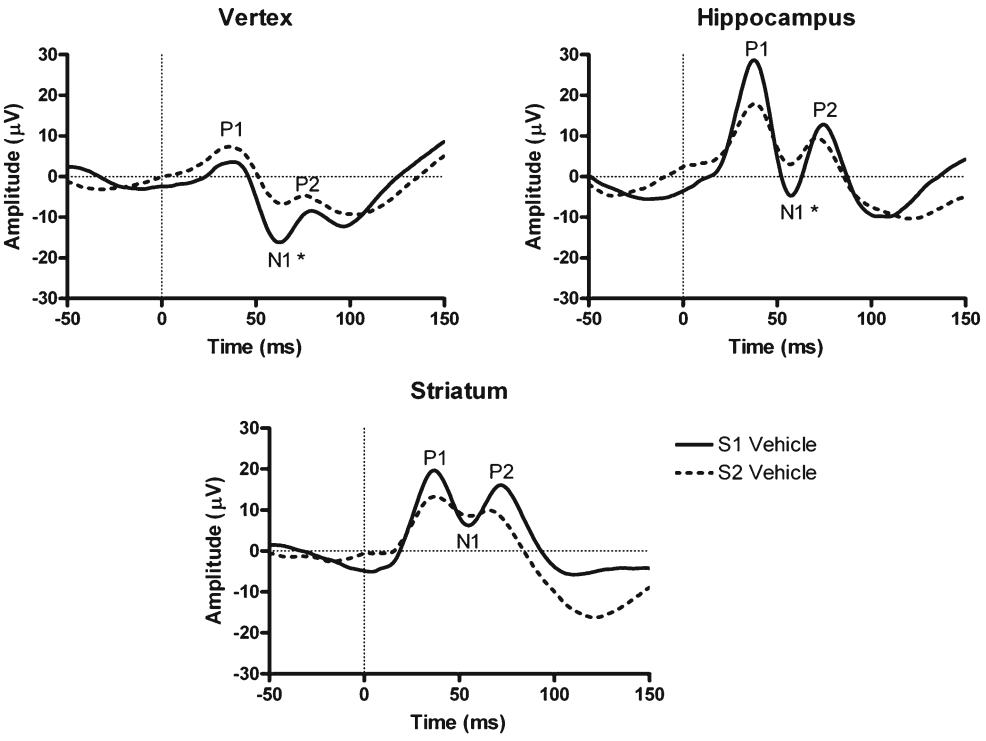

Fig. 1 Effects of placebo (*vehicle*; p.o. 30 min before testing) on grand average ERPs (P1, N1 and P2 component) after the presentation of S1 and S2; effects on gating are depicted with *asterisks* (*$P<0.05$). Latencies are shown on the *x*-axis in milliseconds, amplitudes on the *y*-axis in microvolts. $n_{\text{vertex}}=11$; $n_{\text{striatum}}=11$; $n_{\text{hippocampus}}=13$

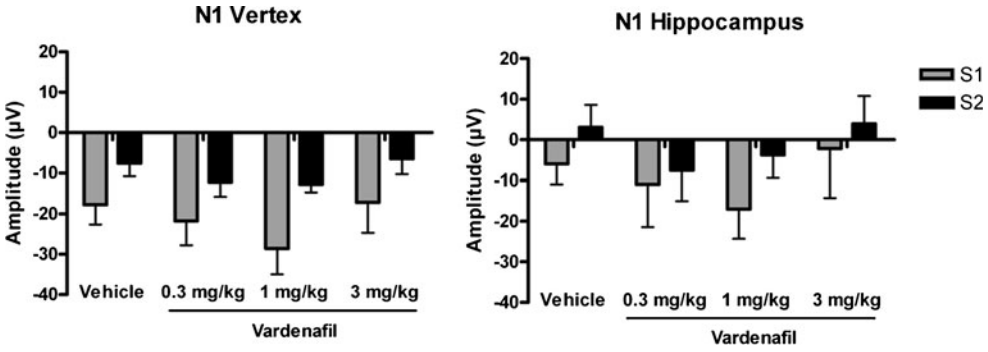

Fig. 2 No effects of treatment with the PDE5-I vardenafil on the mean amplitude (±SEM) of N1 in the vertex and N1 in the hippocampus were found (GLM repeated measures). Drugs were given 30 min before testing. Compounds/doses are shown on the *x*-axis; amplitudes are presented on the *y*-axis in microvolts. $N_{vertex}=11$; $n_{hippocampus}=13$

An interaction effect for the P1 was found for stimulus*treatment*channel ($F_{2.18,\ 34.91}=3.72$; $P<0.05$). Additional analyses of the differences between S1 and S2 showed an interaction between treatment condition and channel ($F_{2.18,\ 34.91}=3.72$; $P<0.05$). Post hoc analyses of each channel separately revealed no further effects. Furthermore, an interaction was detected for the N1 for stimulus*condition ($F_{1.43,\ 22.86}=3.98$; $P<0.05$); however, Bonferonni post hoc analysis of the difference between S1 and S2 showed no effect between treatment conditions. No effects of PDE5 inhibition on the P2 peak were found.

Medical questionnaire

An effect of treatment was found on the report of headache ($F_{1.76,\ 28.10}=6.34$; $P<0.01$) and feeling weak ($F_{1.63,\ 26.00}=7.43$; $P<0.01$). Bonferroni post hoc analysis revealed that there was an increase after administration of both vardenafil 10 and 20 mg compared with the placebo condition.

Discussion

The aim of this study was to test the effects of PDE5 inhibition on auditory sensory gating in rats and humans. It was demonstrated that after treatment with placebo the N1 in the vertex and the hippocampus was more negative after S1 than S2 in rats. Additionally, the response to the S2 was smaller than to the S1 at the P1, N1 and P2 peak in humans in the placebo condition. This indicates that our paradigm elicited sensory gating in the rats as well as in the human subjects. However, neither in rats nor in humans an effect of PDE5 inhibition with vardenafil was found on sensory gating.

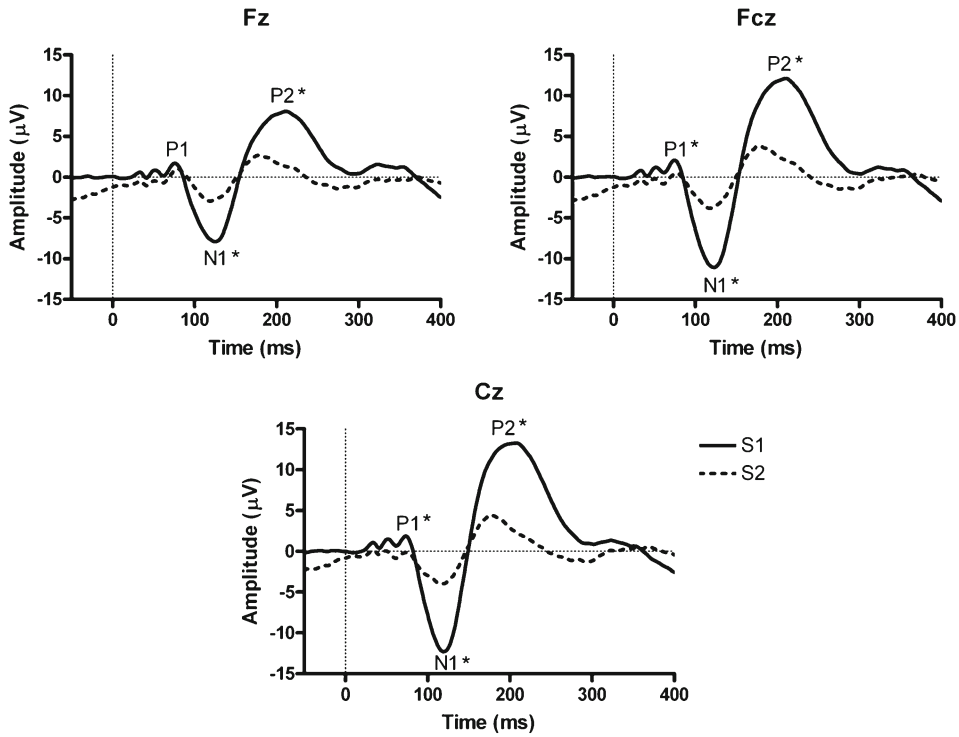

Fig. 3 Effects of placebo treatment (orally 85 min before testing) on grand average ERPs (P1, N1 and P2 component) after the presentation of S1 and S2; effects on gating are depicted with a*sterisks* (*$P<0.05$) ($n=17$). Latencies are shown on the *x*-axis in milliseconds, amplitudes on the *y*-axis in microvolts

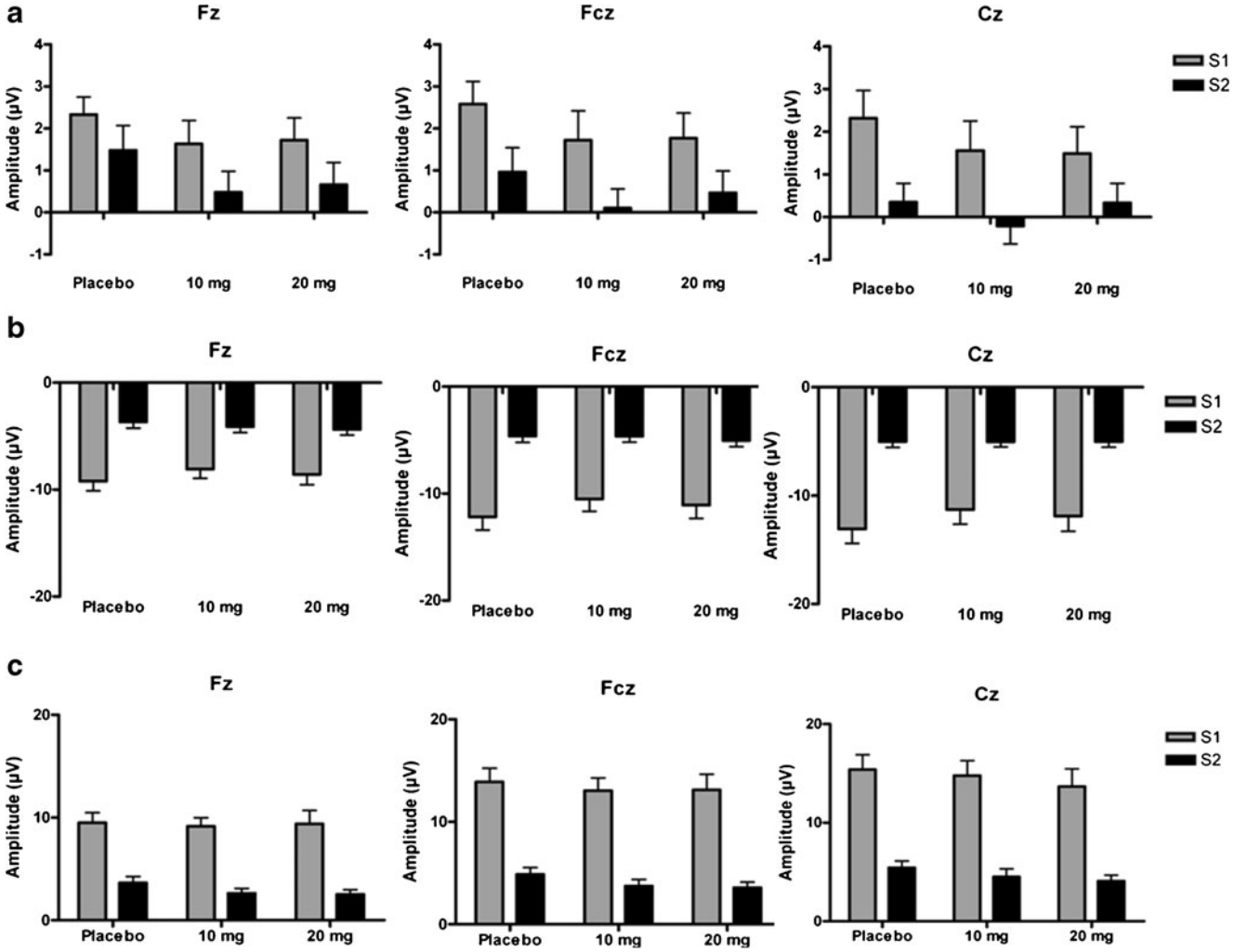

Fig. 4 No effects of treatment with the PDE5-I vardenafil on the mean amplitude (±SEM) of **a** P1, **b** N1 and **c** P2 after the presentation of S1 and S2 were found (GLM repeated measures). Drugs were given 85 min before testing; $n=17$. Compounds/doses are shown on the *x*-axis; amplitudes are presented on the *y*-axis in microvolts

In a recent study (Reneerkens et al. 2012), we showed that vardenafil treatment reversed an MK-801—as well as a scopolamine-induced memory deficit in the object recognition task in rats at a dose of 1 and 1–3 mg/kg, respectively. Vardenafil was administered orally 30 min before testing, similar to our present sensory gating study. To verify the assumption that vardenafil crosses the blood–brain barrier in these animals, blood plasma and brain tissue concentration of 3 mg/kg vardenafil were determined 30 min after oral treatment. It was found that vardenafil had a brain-to-plasma ratio (*Cb/Cp*) of 0.11. The approximate cerebral blood volume relative to total unperfused brain volume is 0.04 (Hitchcock and Pennington 2006), thus a *Cb/Cp* of >0.04 indicated that vardenafil was brain penetrant. In addition, to determine whether there was enough vardenafil present in the brain to be biologically active, we calculated the free brain concentration to meaningfully compare this data to the IC_{50} value of the compound (0.1 nM). The free brain concentration was calculated using vardenafil's molecular weight and its free fraction in plasma and brain homogenate. The free brain concentration of 3 mg/kg vardenafil was 0.4 nM, which is four times its IC_{50} value. This suggests that the 1 and 3 mg/kg doses of vardenafil used in the present study have sufficient biological activity, i.e. PDE5 inhibition. The dose of 0.3 mg/kg vardenafil would have a relatively low biological activity of 0.4 times the IC_{50} but apparently still enough to be biologically active and to improve memory function as previously found in the object recognition task (Prickaerts et al. 2002a). It may thus be concluded that the doses of vardenafil we used in this study should have been expected to be active under the conditions tested.

As mentioned before, it has been shown that PDE5-Is improve cognition in a variety of behavioural tasks in rodents and monkeys (for overview, see Reneerkens et al. 2009). Yet, although the effects of PDE5 inhibition on cognition (especially learning and memory) have been

widely investigated in rodents, little is known about the effects on EEG measurements, including ERPs. However, the results of our current study indicate that the positive effects of PDE5-Is in healthy adult rats might be mediated by affecting higher cognitive processes instead of early basic processes such as sensory gating.

Grass et al. (2001) studied the effects of sildenafil treatment on seven different psychophysical tasks measuring among others short-term memory and divided attention in healthy human subjects. Although PDE5 inhibition showed some effects in reaction time tests, no effects on the cognitive tasks were found. Interestingly, in a recent study of Shim et al. (2011) repeated dosing of the PDE5-I udenafil improved performance on the Korean version of the mini-mental state examination and an assessment battery addressing frontal executive functioning in patients suffering from erectile dysfunction. However, another study (Goff et al. 2009) investigating the effects of sildenafil administration in patients with schizophrenia did not show an effect on cognitive performance. The effects of sildenafil on positive and negative symptoms of schizophrenia were also investigated, but no changes in symptoms were found. In contrast, Akhandzadeh et al. (2011) demonstrated that sildenafil when combined with the atypical antipsychotic risperidone increased the latter's effectiveness in reducing the negative symptoms in patients with schizophrenia. Furthermore, it was shown in healthy subjects that although sildenafil treatment did not improve the behavioural response in attention and word recognition tasks, it did have an effect on EEG measurements (Schultheiss et al. 2001). During the auditory selective attention task, sildenafil elicited EEG responses indicative for an improvement of attention. No effects on ERP measurements related to word recognition were found, although a reduction in negativity of these measurements between 150 and 250 ms after stimulus presentation was found in the word recognition task. The role of this negative deflection in word recognition is not clear, but the authors suggest that 'there is an effect of sildenafil on cerebral information processing'. In our current study, we did not find an effect of PDE5 inhibition on a more specific part of information processing, namely sensory gating. However, the participants did report an increase in headache, which is one of the most commonly reported side effects (≥10 % of the subjects participating in clinical trials) after vardenafil treatment (EMEA 2008) and feeling weak after the administration of 10–20 mg vardenafil compared with the placebo condition on a questionnaire about medical complaints. This indicates that vardenafil is at least bioactive at the dosages and time frame used in our sensory gating study. This would also be confirmed by previous pharmacokinetic data (EMEA 2008) which showed that the maximum plasma concentrations of vardenafil after oral dosing are reached within 30–120 min (median, 60 min); our time point of testing after 85 min is well within this period when also side effects were reported. Additionally, when we take into account the body surface area and the body weight to extrapolate the animal dose to the human dose using the formula of Reagan-Shaw et al. (2008), the doses of 0.3–3 mg/kg in rats should be equivalent to 3–31 mg in our human participants. This indicates that the 10 and 20 mg dosages of vardenafil used in our human experiment are equivalent to the doses, i.e. higher than 1 mg/kg, which have been shown to exert positive effects on cognition in previous animal studies (e.g. Prickaerts et al. 2002b; Reneerkens et al. 2012) and which we also used in the present animal experiment. Thus, although we did not find an effect of vardenafil on sensory gating, the compound can be assumed to be bioactive. So, the effects of PDE5-Is on EEG measures seem to be task dependent and might affect different parts of information processing as we used a sensory gating paradigm to measure the effects on basic auditory information processing, whereas Schultheiss et al. (2001) found the effect in a word recognition task after treatment with 100 mg sildenafil. It cannot be ruled out completely that stimulus salience might have had an effect on the ability to detect drug effects as well since there are sensory gating studies in which the stimuli did not exceed 15–20 dB above background noise levels in animals (Halene and Siegel 2008) and humans (Cadenhead et al. 2005). However, based on previous experiments in our lab (e.g. Sambeth et al. 2007) and a wide variety of sensory gating studies in animals (e.g. Mears et al. 2006; Sambeth et al. 2003; Zhou et al. 2008) as well as humans (Dalecki et al. 2011; Jessen et al. 2001; Lijffijt et al. 2009) which used stimulus parameters similar to ours, it is unlikely that stimulus salience affected our results.

To summarise, the PDE5-I vardenafil did not affect basic auditory information processing tested in a sensory gating paradigm in rats or humans. These findings imply that the positive effects of PDE5 inhibition previously found in both species are possibly the result of positive effects on higher cognitive functions specifically (e.g. memory or attention) instead of on more basic processes involved in a variety of cognitive domains (e.g. basic auditory processing). To further elucidate the effects of PDE5 inhibition on cognition, identical deficit models in animals and humans (e.g. scopolamine or ketamine) should be used in a translational setting. In addition, testing the effects of PDE5-Is on cognitive performance and EEG measurements in a patient population suffering from cognitive dysfunction (e.g. patients with schizophrenia and patients suffering from dementia) is likely to provide further insight into the cognition-enhancing potential of PDE5 inhibition.

Conflicts of interest None

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